UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/891,615	06/27/2001	Ian Duncan Rubin	013306-5003	8850

9629 7590 03/09/2004

MORGAN LEWIS & BOCKIUS LLP
1111 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20004

EXAMINER	
FLOOD, MICHELE C	

ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 03/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

(Rev. 10/03)

Office Action Summary	Application No.	Applicant(s)	
	09/891,615	RUBIN ET AL.	
	Examiner	Art Unit	
	Michele C. Flood	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) *13-24,26-28,31 and 33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,25,29,30,32 and 34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/02,3/02,2/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of the species of the plant genus *Hoodia* on December 12, 2003 is acknowledged.

Further acknowledgment is made of Applicant's identification of Claims 1-12, 25, 29-30, 32 and 34 as encompassing the elected species *Hoodia*.

The originally elected species of *Hoodia* was not found, therefore the requirement for species election has been withdrawn. The Claims were examined on the merits taking each of the species of *Hoodia* and *Trichocaulon* into consideration.

Claims 1-12, 25, 29, 30, 32 and 34 are under examination.

Specification

At present the title of the application recites, "Extracts, Compounds & Pharmaceutical Compositions having Anti-diabetic Activity and their Use". It is suggested that Applicant delete "&", and add and to place the title in proper grammatical form.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-12, 18, 25, 29, 30, 32 and 34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating and reducing the risk of development of non-insulin dependent type II diabetes in a mammal comprising administering to a mammal in need in thereof an effective dose of an extract of a plant of the genus *Trichocaulon* or of the genus *Hoodia* and wherein the claim-designated plant extract comprises a disclosed compound of the structural formula (I), does not reasonably provide enablement for treating or preventing any and all types of diabetes in a mammal comprising the administration of any and all extracts of the claim-designated plant extracts to any and all mammals, as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to a method of treating or preventing diabetes by administering to a human or animal an effective dosage of an extract of the genus *Trichocaulon* or of the genus *Hoodia*. The claims are further drawn to a method according to claim 1, wherein said plant of the genus *Trichocaulon* is selected from the group consisting of *Trichocaulon piliferum* and *Trichocaulon officinale* and said plant of the genus *Hoodia* is selected from the group consisting of *Hoodia currorri, Hoodia*

gordonii and *Hoodia lugardii*. The claims are further drawn to a method according to claim 1, wherein the extract is obtainable by a process comprising the steps of treating collected plant material with a solvent to extract a fraction having anti-diabetic activity, separating the extraction solution from the rest of the plant material, removing said solvent from said extraction solution and recovering said extract. The claims are further drawn to a method according to claim 3, wherein the process further comprises the step of concentrating the active agent in the extracted material by further of concentrating the active agent in the extracted material by further extraction with a solvent; wherein said solvent of said solvent extraction step or steps is one or more of methylene chloride, water, methanol, hexane, ethyl acetate or mixtures thereof. The claims are further drawn to a method according to claim 3, wherein the process further comprises the step of concentrating the active agent in the extracted material by chromatographic separation employs one or more of chloroform, methanol, ethyl acetate, hexane or mixtures thereof as an eluant. The claims are further drawn to a method according to claim 6, wherein the process includes carrying out the chromatographic separation on a column, collecting the eluate in fractions from the column, evaluating the fractions to determine their anti-diabetic activity, and selecting at least one fraction containing the anti-diabetic agent. The claims are further drawn to a method according to claim 1, wherein said extract is obtainable by a process comprising the steps of pressing collected plant material to separate sap from solid plant material and recovering the sap from of the solid plant material to form the extract; wherein said extract is processed to from a free-flowing powder; wherein said extract comprises the compound of illustrated

general formula (1); and, wherein said extract is administered in a foodstuff or beverage to have an anti-diabetic effect when ingested. Applicant claims a method of treating or preventing diabetes comprising the step of administering to a human or animal an effective dosage of I) an extract of plant of the genus T*richocaulon* or of the genus *Hoodia* or at least one compound of formula (A), (1), (2), (3), (4), (5), (6), (7), (8), (9), (10), (11), (12), (13) or (14) in association with ii) one or more other agents chosen from: representative agents to treat diabetes, glycogen phosphorylase inhibitors, sorbitol dehydrogenase inhibitors, glucosidase inhibitors and aldose reductase inhibitors. Applicant further claims the method of claim 32, wherein the ingredients i) and ii) are simultaneously, separately, or sequentially administered.

The factors to be considered in determining whether undue experimentation is required are summarized in In re Wands, 858 F.2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of one of ordinary skill in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) the quantity of experimentation added to make or use the invention based on the content of the disclosure. While all of these factors are considered, a sufficient number are discussed below so as to create a *prima facie* case.

While the specification does reasonably demonstrate orally administering effective amounts of an extract of a plant of the genus *Trichocaulon* or of the genus *Hoodia* comprising a disclosed compound of the structural formula (I) to a mammal in need thereof *per se*, the specification does not demonstrate administering the

aforementioned composition for treating much less preventing any and all types of diabetes in any and all mammals comprising the administration of any and all extracts of the claim-designated plant extracts, as broadly claimed. For example, on page 26, lines 8-11, Applicant discloses an active ingredient found in an extract of either *Trichocaulon* or *Hoodia*: "The Applicant has found that at least one purified fraction has good anti-diabetic activity, and the active principle in the fraction was identified by conventional chemical techniques including nuclear magnetic resonance, and was found to be a compound of the structural formula (1) as shown above [referring to compound of the general formula (1) as set forth on page 2 of the present specification]." On page 25, line 1 to page 26, line 11, Applicant discloses a method of making one fraction having the claim-designated functional effect of anti-diabetic activity encompassing treating *Trichocaulon* or *Hoodia* plant material, namely stems and roots, with solvents, such as methanol/methylene chloride, *etc.* On page 15, lines 2-8, Applicant discloses advantageously administering effective dose amounts of an anti-diabetic agent comprising a compound of formula (1) to mammals to provide treatment of diabetes. With regard to the treatment of diabetes, the Office notes that Applicant discloses administering an effective amount of the aforementioned compound to inbred ZDF/Gmi rats (a recognized animal model for non-insulin dependent diabetes in humans) resulted in a reduction in the blood glucose concentration from the diabetic level to a similar concentration as in lean littermates after 7 days of treatment; and, maintaining normal glycemia in rats until withdrawal of therapy when blood glucose levels increased in a similar manner in treated rats and control rats, on page 36, lines 8-14. Applicant

further discloses that the administration of the aforementioned compound to the test model rats provided the beneficial effects for water and food intake reduction, marginally reducing impaired glucose tolerance, and minimal weight gain, as compared to their lean littermates and/or pair-fed controls. While Applicant discloses that the differences between the treated animals and the lean littermate and/or pair-fed control were not significantly different, it is not apparent from Applicant's disclosure how much difference of was measured in the responses of the treated and untreated groups since Applicant provides no comparative data. The Office further notes that while Applicant discloses treatment with the aforementioned compound to ZDF rats at 6 weeks of age (*i.e.*, pre-diabetic ZDF rat model) resulted in maintenance of normal glycemia until withdrawal of therapy, it is not clear from Applicant's disclosure the length of the treatment of the pre-diabetic animal models.

Inventions targeted for therapy in living subjects should provide evidence because of the unpredictability in biological responses to therapeutic treatments. Claims drawn to pharmaceutically acceptable compositions and methods of administering compounds to living subjects which would in effect 'prevent' the condition from happening require supporting evidence which clearly define the ingredients or constituents therein and supporting data because of the unpredictability in biological responses to therapeutic treatments or therapeutic prophylaxis. In order to enable the skilled artisan to practice the invention as claimed, Applicant would have to demonstrate the functional effect and describe the therapeutic effect or prophylactic effect, and describe the effective amounts of each ingredient for the administration of

the composition intended for a therapeutic treatment or prophylaxis. Moreover, the state of the art at the time the invention was filed did not recognize the treatment of either Type I diabetes mellitus or nephrogenic diabetes insipidus in the same manner as the treatment of Type II diabetes, which is the subject matter to which Applicant directs the claimed invention. *See The Merck Manual*, pages 165-185 and page 1902. Yet, Applicant broadly claims that the administration of the claim-designated plant extracts to either a human or an animal is effective in the treatment and prevention of any and all diabetes. Even Applicant readily admits on page 37, lines 5-6, that the ZDF/Gmi is a model of non-insulin dependent diabetes. Moreover, Applicant readily admits on page 37, line 21 to page 38, line 11, "The first-line treatment for non-insulin dependent diabetes in man is diet plus exercise." Applicant further discloses, "If body weight can be reduced by 5 kg then a marked improvement in diabetic control can be achieved." Thus, while Applicant may have reasonably demonstrated that the oral administration of the claim-designated plant extracts comprising the aforementioned formula (1) to ZDF/Gmi rats reduces water and food intake, and consequently reduces weight, blood glucose concentration and glucose intolerance, there is no guidance in the specification for the prevention of non-insulin dependent type I diabetes much less prevention of any and all diabetes in any and all animals and/or humans comprising the instantly claimed method. Moreover, the instant application does not provide a working example providing data which shows that the composition of the instant claims would indeed prevent or eliminate the claim-designated disease condition. Thus, Applicant has not demonstrated a method for treating much less preventing any and all types of diabetes

in either an animal or a human comprising the administration of any and all extracts of the claim-designated plant extracts of either T*richocaulon* or *Hoodia*, as broadly claimed, other than the aforementioned and demonstrated treatment of non-insulin dependent type II diabetes comprising the administration of effective amounts of the claim-designated plant extracts comprising formula (1) to a mammal in need thereof.

Accordingly, it would take undue experimentation without a reasonable expectation of success for one skill in the art to prepare a pharmaceutical composition from the claimed ingredients which have the functional effect for preventing and/or treating any and all types of diabetes in any and all mammals, as broadly claimed by Applicant.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-12, 18, 25, 29, 30, 32 and 34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is rendered vague and indefinite by the term "extract" because this term, in and of itself, does not adequately delineate its metes and bounds. This term is best defined as a product-by-process since product-by-process claims are intended to define products which are otherwise difficult to define (and/or distinguish from the prior art). For example, is the extract obtained via extraction with water, a polar solvent, a non-

polar solvent, an acid or base, a squeezed extract, or something else? In addition, from what part(s) of the plant is the extract obtained? It is well accepted in the herbal art that extraction with one of various distinct solvents, as well as from particular parts of therapeutic plants, has a profound impact on the final product with respect to the presence, absence, amounts, and/or ratios of active ingredients therein and, thus, its ability to provide the desired functional effect(s) instantly claimed and/or disclosed. Since the extract itself is clearly essential to the claimed invention, the step(s) by which the claimed extract is obtained are also clearly essential and, therefore, must be recited in the claim language itself (i.e., as a product-by-process). Please note that although the claims are interpreted in light of the specification, critical limitations from the specification cannot be read into the claims (see, e.g., *In re* Van Guens, 988 F.2d 1181, 26 PSPG2d 1057 (Ded. Cir. 1991)). Accordingly, without the recitation of all these critical limitations as set forth above, the claims do not adequately define the instant invention.

Claim 8 recites the limitation "the eluate" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claim 8 recites the limitation "the anti-diabetic agent" in 4. There is insufficient antecedent basis for this limitation in the claim.

The metes and bounds of Claim 11 are made uncertain by “pro-drugs” because it is unclear as to what constitutes a “pro-drugs” or how closely related the “pro-drug” must be to considered a “pro-drug” of the illustrated compound of general formula (1). A derivation of a chemical compound or a pro-drug or a chemical compound may be

closely patterned after the subject chemical compound or may be loosely patterned after the subject chemical compound, such that it may bear no resemblance or form recognizable as the subject chemical compound which maybe chemically and/or biologically unrelated in function or form to the subject chemical compound. The lack of clarity renders the claim ambiguous.

All other cited claims depend directly or indirectly from rejected claims and are, therefore, also, rejected under U.S.C. 112, second paragraph for the reasons set forth above.

Claim Objections

Claim 18 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim, or amend the claim to place the claim in proper dependent form, or rewrite the claim in independent form. In the instant case, Claim 18 fails to further limit the claimed subject matter because Claim 18 depends from non-elected Claim 16.

Claim 25 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim, or amend the claim to place the claim in proper dependent form, or rewrite the claim in independent form. In the instant case, Claim 25 fails to further limit the claimed subject matter because Claim 25 depends from non-elected Claims 14 and/or 20.

Claim 30 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim, or amend the claim to place the claim in proper dependent form, or rewrite the claim in independent form. In the instant case, Claim 30 fails to further the claimed subject matter because Claim 30 depends from claim 31. A claim cannot depend from a claim that follows it.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michele C. Flood whose telephone number is (571) 272-0964. The examiner can normally be reached on 7:00 AM - 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Michele C. Flood

MICHELE FLOOD
PATENT EXAMINER

MCF
March 8, 2004